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# Health and Environmental Effects Profile for Chloronitrobenzenes

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16. ABSTRACT

The Health and Environmental Effects Profile for chloronitrobenzenes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for chloronitrobenzenes.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.


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# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CHLORONITROBENZENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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# PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of $q_1^*$ (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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## LIST OF ABBREVIATIONS

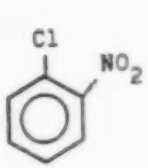
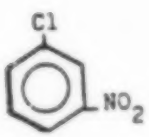
| | |
|---|---|
| ADI | Acceptable daily intake |
| BCF | Bioconcentration factor |
| bw | Body weight |
| DNA | Deoxyribonucleic acid |
| GC | Gas chromatography |
| i.p. | Intraperitoneal |
| $LC_{50}$ | Concentration lethal to 50% of recipients |
| MED | Minimum effective dose |
| ppm | Parts per million |
| RQ | Reportable Quantity |
| s.c. | Subcutaneous |
| TWA | Time weighted average |

# 1. INTRODUCTION

Chloronitrobenzenes (CNBs) are a class of compounds formed by nitrating chlorobenzene (Windholz, 1976). Production of CNBs is a primary use of chlorobenzene. The reaction based on deactivation of all of the ring position ch chlorine substitutions, results in three isomers, o-, m- and p-CNB, with yields of 29.6, 0.9 and 68.9%, respectively (Roberts and Caserio, 1964). As m-CNB production is not significant in this reaction it is also manufactured by the chlorination of nitrobenzene in the presence of a catalyst (Windholz, 1976).

## 1.1. STRUCTURE AND CAS NUMBER

The structural and empirical formulae, CAS Registry numbers and common synonyms of o-, m- and p-CNB are as follows (Windholz, 1976):

| | o-CNB | m-CNB | p-CNB |
|---|---|---|---|
| Structural: |  |  | |
| Empirical: | $C_6H_4ClNO_2$ | $C_6H_4ClNO_2$ | $C_6H_4ClNO_2$ |
| CAS Registry No.: | 88-73-3 | 100-00-5 | 121-73-3 |
| Synonym: | 1-Chloro-2-nitrobenzene | 1-Chloro-3-nitrobenzene | 1-Chloro-4-nitrobenzene |

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of o-, m- and p-CNB are presented in Table 1-1.

## 1.3. PRODUCTION DATA

1.3.1. Production Data for o-CNB. The U.S. EPA TSCA Production Inventory (1980) lists the domestic producers of o-CNB in 1977, with a total United States production of 13-80 million pounds (Table 1-2).

TABLE 1-1

Physical and Chemical Properties of o-, m- and p-CNB

| | o-CNB | m-CNB | p-CNB |
|---|---|---|---|
| Molecular weight[a] | 157.6 | 157.6 | 157.6 |
| Melting point (°C)[b] | 32-33 | 46 | 82-84 |
| Boiling point (°C)[b] | 245-246 | 236 | 242 |
| Specific gravity[a] | 1.368 | 1.534 | 1.520 |
| Water solubility (g/ℓ)[c] at 20°C | 0.441 | 0.273 | 0.453 |
| Vapor pressure (mm Hg)[a] | 10 (230°F) | NA | 0.0128[d] |
| Octanol/water[a] partition coefficient (log of) | 2.24 | 2.41 | 2.41 |

[a]Howard et al., 1976

[b]Windholz, 1976

[c]Eckert, 1962

[d]Freed and Hagne, 1976 (at unspecified temperature)

NA = Not available

TABLE 1-2

Major Producers of o-CNB*

| Producer | Location | Production Volume (million pounds) |
|---|---|---|
| FMC Corporation | Philadelphia, PA | no report |
| Monsanto | Sauget, IL | 1-10 (not confined to site)<br>10-50 (confined to site) |
| Aceto Chemical | Flushing, NY | 0.01-0.1 |
| American Hoechst Corp. | Bridgewater, NY | no report |
| Prochimie International | New York, NY | 1-10 |
| E.I. duPont de Nemours | Deepwater, NJ | 1-10 (confined to site)<br>importer<br>0.01-0.1 (not confined to site) |

*Source: TSCA Inventory, 1980

The Directory of Chemical Producers (SRI, 1984) and USITC (1983) identify only two current domestic manufacturers of o-CNB, E.I. duPont de Nemours (Deepwater, NJ) and Monsanto (Sauget, IL). Production volume data were not available.

1.3.2. Production Data for m-CNB. The U.S. EPA TSCA Inventory (1980) lists the Eastman Kodak Company as the only manufacturer of m-CNB. No production data were reported for 1977. The Directory of Chemical Producers (SRI, 1984) and USITC (1983) do not identify any current domestic manufacturers of m-CNB. As m-CNB is a product of nitrating chlorobenzene (the principal method of manufacturing o- and p-CNB), manufacturers of o- and p-CNB are expected to produce very small quantities (see Introduction) of m-CNB.

1.3.3. Production Data for p-CNB. The U.S. EPA TSCA Inventory (1980) identifies two manufacturers of p-CNB in 1977. E.I. duPont de Nemours and Company of Deepwater, NJ produced an unreported amount of p-CNB. Monsanto Company of Sauget, IL produced 50-100 million pounds. The Directory of Chemical Producers (SRI, 1984) and USITC (1983) also identifies these firms as the only current domestic producers of p-CNB. SRI (1984) estimates current yearly domestic production capacity at 130 million pounds, 45 million pounds by E.I. duPont de Nemours and 85 million pounds by Monsanto.

1.4. USE DATA

1.4.1. Use Data for o-CNB. The Merck Index (Windholz, 1976) indicates that o-CNB is used as a chemical intermediate particularly in the dye manufacturing industry. Windholz (1976) also reported that o-CNB is used in the manufacture of 1-chloro-2,4-dinitrobenzene.

1.4.2. Use Data for m-CNB. Verschueren (1983) reported that m-CNB is used as an intermediate in the manufacture of dyestuffs and other organic chemicals.

1.4.3. Use Data for p-CNB. 4-Chloronitrobenzene is used as an intermediate in the manufacture of a number of organic compounds including: amide and carbamate pesticides, parathion, drugs, dyes antioxidants and oil additives. In 1977, 50% of the p-CNB produced was used in the manufacture of parathion (SRI, 1977). It is also used in the sythesis of 4-acetylaminophenol, more commonly known as Tylenol (SRI, 1980).

## 2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

### 2.1. AIR

Kanno and Nojima (1979) investigated the photochemical reactions of o-, m- and p-CNB in air and nitrogen free of nitrogen oxides. The compounds were irradiated for 5 hours with a xenon lamp in glass and quartz reaction vessels. The amount of parent compound remaining after exposure, and the type and proportion of the resulting degradation products varied considerably depending on the type of reaction vessel used. The primary reaction products identified in air in Pyrex glass vessels were as follows:

| | | |
|---|---|---|
| o-CNB | - | 2-Chloro-6-nitrophenol |
| | - | 2-Chloro-4-nitrophenol |
| m-CNB | - | 3-Chloro-2-nitrophenol |
| | - | 3-Chloro-6-nitrophenol |
| | - | 3-Chloro-4-nitrophenol |
| p-CNB | - | 4-Chloro-2-nitrophenol |

It was also noted that ~1% of the isomers disappeared per hour upon irradiation with a xenon lamp in Pyrex vessels. Therefore, photochemical degradation is likely to be a slow process in the air.

### 2.2. WATER

The hydrolysis of p-CNB was investigated by Bhave and Chandalia (1976) under rigorous conditions. A mixture of stoichiometric amounts of sodium hydroxide and p-CNB in water was agitated for 6 hours at 120°C. Only 25% of the original compound was hydrolyzed under these extreme conditions. Therefore, p-CNB is expected to be resistant to hydrolysis under ambient conditions. Information provided by Parris (1980) indicates that o-CNB did not hydrolyze in aqueous solutions (pH 7-8) stored at room temperature for 17 days. Specific data concerning the hydrolysis of m-CNB were not encountered in the available literature.

Kramer (1965) found that o-CNB was persistent along a 1450 km portion of the Mississippi River (from St. Louis to the Gulf). Reductions in the measured concentration of the compound were explained completely by dilution factors. These findings suggest that o-CNB was not degraded during the unspecified amount of time required to travel the 1450 km.

Zoeteman et al. (1980) estimated half-life values for o-, m- and p-CNB in the Rhine River from monitoring data collected in the Netherlands. The estimated half-life values were 3.2, 2.6 and 0.9 days for o-, m- and p-CNB, respectively. The half-life of p-CNB in groundwater aquifers was also estimated to be between 3 and 30 days.

Ludzack and Ettinger (1963) investigated the fate of o-CNB in Ohio River water supplemented with weekly additions of settled sewage. The amount of biodegradation was assessed from $CO_2$ evolution. No degradation was observed after incubation periods as long as 175 days. The presence of o-CNB was confirmed after incubation using infrared spectroscopy. Unfortunately, this method of confirmation is not sensitive enough to separate closely related aromatic metabolites from the parent material.

A number of investigators have examined the biodegradability of p-CNB. Alexander and Lustigman (1966) found that p-CNB did not degrade in water inoculated with microorganisms obtained from soil. The initial concentration was 10 µg/mℓ and the test duration was 64 days. Both Kitano (1978) and Sasaki (1978), using activated sludge systems, classified o- and p-CNB as nondegradable. Other investigators, however, found o- and p-CNB biodegradable with certain mixed cultures of microorganisms. For example, adapted activated sludge decomposed 99% of o- and p-CNB in industrial wastewaters containing ≤100 mg/ℓ of the compounds (Jakobczyk et al., 1981). A biological film settled in an immersed disk bed was also used to biodegrade

both o- and p-CNB in wastewaters with high efficiency (>99%) (Jakobczyk et al., 1984). The para-isomer present in wastewaters at concentrations ≤0.05 mg/ℓ also was degraded completely by adsorbed microorganisms under laboratory anaerobic conditions (Gvozdyak et al., 1982).

The biogradability of CNB isomer by pure cultures has been demonstrated by several authors. The results of Bielaszczyk et al. (1967) indicate that p-CNB is degraded readily by pure cultures of Arthrobacter simplex and other microbes isolated from garden and forest soils and industrial wastewaters. Degradation as high as 91% was observed in 12-day incubation periods. The principal metabolite was identified as p-chloroaniline. Corbett and Corbett (1981) also found that p-CNB was degraded in 14 days using a pure culture of Rhodosporidium sp. The major metabolite was also identified as p-chloroaniline. Likewise, Gvozdyak et al. (1983) showed that nonadapted cultures of E. coli were capable of transforming p-CNB into p-chloroaniline.

It is difficult to assess the biodegradation potential of CNB isomers in natural waters from the preceding discussion. It seems likely that these compounds will not biodegrade significantly in most natural water bodies (Howard et al., 1982; Piet and Zoeteman, 1980).

Data pertaining to the volatility of CNB isomers from aquatic media were not available.

## 2.3. SOIL

In a study designed to examine the effectiveness of various drinking water purification methods in the Netherlands, Zoeteman et al. (1980) and Piet and Morra (1983) indicated that o-, m- and p-CNB were effectively removed from Rhine River water and groundwater by both bank and dune infiltration. Parris (1980) reported that the amino groups formed in the environment from aromatic nitro compounds and other amines can react with soil

organic matter and form bound residues. More quantitative data regarding the absorption and degradation of o-, m- and p-CNB in soil and sediments were not encountered in the available literature.

In summary, most of the available information indicates that o-, m- and p-CNB are resistant to hydrolysis and biodegradaton in the aquatic environment. These compounds may adsorb to soils or sediments but are likely to persist in the aquatic environment.

## 3. MONITORING

Monitoring data for o-, m- and p-CNB are not extensive. STORET contains 1 record for o-CNB and 2 records for m-CNB. o-CNB was detected at a concentration of 0.2 mg/kg in sediments of Ellicott Creek near the confluence with the Niagara River in Buffalo, NY. m-CNB was detected in two sediment samples collected in the northeast portion of Lake Ontario. The concentrations observed were 0.7 and 320 mg/kg sediment.

The concentrations of o-, m- and p-CNB in Rhine water in the Netherlands were reported to be 0.001 mg/ℓ, 0.003 mg/ℓ and 0.001 mg/ℓ, respectively (Piet and Zoeteman, 1980). None of these compounds were detected after treatment of this surface water by sand filtration with a residence time of several years and dune filtration with an average residence time of 2 months (Piet and Zoeteman, 1980). In a Russian study (Zetkin et al., 1973), o-, m- and p-CNB were detected in wastewaters from a m-CNB production facility at concentrations ranging from 100-200, 500-700 and 10-30 mg/ℓ, respectively. In the United States unspecified CNB isomers were detected at concentrations >0.001 mg/ℓ in 10% of water samples collected from the Delaware River and its tributaries near the Trenton/Philadelphia/Wilmington area (Dewalle and Chian, 1978). The meta-isomer was identified but not quantified in the treated drinking water from the Carrollton and Jefferson Parish No. 1 treatment plants in New Orleans; however, a second U.S. EPA laboratory did not detect the compound in the same water (Keith et al., 1976).

Bioconcentration factors calculated from the octanol/water partition coefficients (see Table 1-1) using the equation of Veith et al. (1980) are 22, 27 and 27 for o-, m- and p-CNB, respectively. Although these BCF values are not substantial, residues of o-, m- and p-CNB have been detected in

fish, which is probably due to the persistence of these compounds in the aquatic environment. Yurawecz and Puma (1983) detected residues of o-, m- and p-CNB in the edible portion of Mississippi River fish. The residue levels observed by these authors are presented in Table 3-1.

TABLE 3-1

Chloronitrobenzene Residues in Mississippi River Fish[a,c]

| Species | Collection Site[b] | o-CNB | m-CNB | p-CNB |
|---|---|---|---|---|
| Catfish | 0 | <0.005 | <0.005 | 0.008 |
| Catfish | 0 | 0.064 | ND[d] | 0.19 |
| Catfish | 0 | 0.053 | ND[d] | 0.088 |
| Catfish | 0 | 0.026 | ND[d] | 0.20 |
| Carp/Sucker[e] | 0 | 0.24 | 0.057 | 0.63 |
| Buffalofish | 60 | 0.12 | ND[d] | 0.20 |
| Catfish | 150 | 0.006 | <0.005 | 0.019 |
| Catfish | 150 | 0.027 | <0.005 | 0.025 |

[a]Source: Yurawecz and Puma, 1983

[b]Fish collection site in miles downstream of St. Louis

[c]Residue in ppm edible portion of fish

[d]GC resolution was inadequate to detect or determine m-CNB in the presence of 10-fold larger amounts of p-CNB. If m-CNB is present in the sample, the concentration is estimated as <10% of that of the p-CNB.

[e]Composite of 2 species

ND = Not detected

## 4. PHARMACOKINETICS

### 4.1. ABSORPTION

Gastrointestinal absorption of the CNBs can be inferred from the results of a study by Bray et al. (1956). Rabbits given a single oral dose (0.2 g/kg) of o-, m- or p-CNB eliminated 82, 63 or 63%, respectively, of the administered dose in the urine within 48 hours of administration. These values do not include the small amounts of phenolic metabolites excreted in unconjugated form (the authors contend that this is probably <5% of the administered dose).

### 4.2. DISTRIBUTION

Pertinent data regarding the distribution of m-CNB were not located in the available literature as cited in Appendix A.

### 4.3. METABOLISM

Bray et al. (1956) reported that the primary steps in the metabolism of m-CNB are hydroxylation and reduction. In the rabbit (see Section 4.1.), phenols and chloroanilines were formed and excreted primarily as conjugates with sulfuric and glucuronic acids. There was little or no acetylation of the chloroanilines that were formed. The hydroxylation reactions were believed to occur either before or after reduction of the nitro-compound. A minor pathway for the metabolism of o- and p- but not m-CNB was reported to result in mercapturic acid formation by acetylcysteyl-dechlorination. A listing of metabolites identified in the urine and feces (pooled samples, 48 hours) of rabbits exposed orally to the monochlorobenzenes is given in Table 4-1.

### 4.4. EXCRETION

Rabbits given a single oral dose (0.2 g/kg) of o-, m- or p-CNB excreted 82, 63 and 63% in the urine, respectively, and 0.3, 0.6 and 2.8% in the feces, respectively (Bray et al., 1956).

TABLE 4-1

Excreted Metabolites of o-, m- and p-CNB[a]

| Metabolite | Mean % of Administered Dose | | |
|---|---|---|---|
| | ortho- | meta- | para- |
| Feces | | | |
| Unchanged parent compound | 0.3 | 0.6 | 2.8 |
| Urine | | | |
| Ether glucuronide | 42 | 33 | 19 |
| Ethereal sulfate | 24 | 18 | 21 |
| Mercapturic acid | 7 | 1 | 7 |
| Chloroaniline (free) | 9 | 11 | 9 |
| Chloroaniline (conjugated) | 0 | 0 | 4 |

[a]Source: Bray et al., 1956

[b]Based on 48-hour urine samples (pooled) from 6 rabbits

## 5. EFFECTS

### 5.1. CARCINOGENICITY

Weisburger et al. (1978) tested the carcinogenic potential of o- and p- CNB in Charles River CD rats and in CD-1 mice derived from strains HaM/ICR. Treatment groups consisted of 25 males and 25 females (mice) or 25 males (rats). Each compound was administered initially in the diet at the maximum tolerated concentration and one-half the maximum tolerated concentration, based on subchronic studies. Changes in concentration were made if weight gain was reduced by 10% in comparison with controls, or if toxic effects were observed. The feeding protocol for both compounds and both species is given in Table 5-1. Specific reasons were not given as to why changes were made. During the first 6 months of the experiment, animals that died were discarded without necropsy. After 18 months of treatment, surviving rats and mice were maintained on control diets for an additional 6 and 3 months, respectively, and then killed. Tissues from lungs, kidneys, liver, spleen, adrenals, heart, bladder, stomach, intestines, reproductive organs, pituitaries (rats only), all tumor masses, and all grossly abnormal organs were examined histologically. In rats, there were no dose-related, significant differences between controls and treated animals with regard to incidences of tumors (individual or combined) for either compound. Male and female mice exposed to p-CNB had significantly increased incidences ($p<0.025$ Fisher's Exact Test, both pooled and matched controls) of unspecified vascular tumors at the highest dose tested (TWA = 673 mg/kg/day). These values are given in Table 5-2. In addition, male mice exposed to p-CNB had an increased incidence of liver tumors ($0.025 \leq p \leq 0.05$, Fisher's Exact Test, pooled controls only), but only at the low dose. Female mice exposed to o-CNB had an increased incidence of hepatocellular carcinoma ($p<0.025$,

TABLE 5-1

Feeding Protocol for Rats and Mice in the Testing of the Carcinogenic Potential of o- and p-CNB*

| Compound | Species | Dietary Concentration in ppm (duration) |
|---|---|---|
| o-CNB | rat | 0, 1000, 2000 (6 mo.); 0, 500, 1000 (12 mo.) |
| | mouse | 0, 3000, 6000 (8 mo.); 0, 1500, 3000 (10 mo.) |
| p-CNB | rat | 0, 2000, 4000 (3 mo.); 0, 250, 500 (2 mo.) 0, 500, 1000 (13 mo.) |
| | mouse | 0, 3000, 6000 (18 mo.) |

*Source: Weisburger et al., 1978

TABLE 5-2

Incidence of Vascular Tumors in CD-1 Mice
Exposed to p-CNB[a,b]

| Sex | Control (matched) | Control (pooled) | Low Dose[c] | High Dose[d] |
|---|---|---|---|---|
| Male | 0/14 | 5/99 | 2/14 | 4/14 |
| Female | 0/15 | 9/102 | 2/20 | 7/18 |

[a]Source: Weisburger et al., 1978

[b]Incidence expressed as number of animals bearing tumors/number of animals examined (surviving >6 months on treatment)

[c]TWA = 337 mg/kg/day

[d]TWA = 673 mg/kg/day

pooled controls only), but only at the low dose. Female mice exposed to o-CNB had an increased incidence of hepatocellular carcinoma ($p<0.025$, Fisher's Exact Test, both pooled and matched controls) at both doses tested (TWA = 243 and 486 mg/kg/day). Male mice exposed to o-CNB had an increased incidence of hepatocellular carcinoma ($0.025 \leq p \leq 0.05$, Fisher's Exact Test, pooled controls only) but only at the lowest dose tested (TWA = 243 mg/kg/day). These data are summarized in Table 5-3.

According to proposed EPA quidelines (1984) the o- and p-isomers of chlorinated nitrobenzenes could be classified as 132 compounds.

Pertinent data regarding the carcinogenicity of m-CNB were not located in the available literature as cited in Appendix A.

## 5.2. MUTAGENICITY

Data relevant to the mutagenicity of o-CNB in Salmonella typhimurium are summarized in Table 5-4. Both o-CNB and p-CNB have been reported mutagenic in one or more strains of Salmonella (D'Addario and Jagganath, 1981; Shimizu et al., 1983; Suzuki et al., 1983). Only m-CNB was consistently negative in all studies.

The genotoxic effects of p-CNB have also been investigated in two eukaryotic systems. DNA breakage was observed in the brains, kidneys, and livers of mice that had been injected intrapertioneally with 30, 60, 180 or 1000 mg p-CNB/kg bw (Cesarone et al., 1983). A concentration of $5 \times 10^{-4}$ M p-CNB, however, did not cause the scission of protein from DNA in cultured mouse fibroblasts (Andoh et al., 1975); however, the significance of this finding is unclear.

## 5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of o-, m- or p-CNB were not located in the available literature as cited in Appendix A.

TABLE 5-3

Incidence of Hepatocellular Carcinoma in CD-1 Mice Exposed to o-CNB[a,b]

| Sex | Control (matched) | Control (pooled) | Low Dose[c] | High Dose[d] |
|---|---|---|---|---|
| Female | 0/20 | 1/102 | 5/22 | 5/19 |
| Male | 3/18 | 7/99 | 7/17 | 3/16 |

[a]Source: Weisburger et al., 1978

[b]Incidence expressed as number of animals bearing tumors/number of animals examined (surviving >6 months on treatment)

[c]TWA = 243 mg/kg/day

[d]TWA = 486 mg/kg/day

TABLE 5-4

Mutagenicity of the m-CNB in Salmonella typhimurium

| Strain | Dose | Compound | Metabolic Activation | Response | Reference |
|---|---|---|---|---|---|
| TA100 | NR | o-CNB | +S9 | + | D'Addario and Jagannath, 1981 |
| | | p-CNB | +S9 | + | |
| | | m-CNB | +S9 | - | |
| TA98, 1537, 1538 (frameshift) | 0-3276.8 µg/plate | o-CNB | - | + | Shimizu et al., 1983 |
| | | p-CNB | - | - | |
| | | m-CNB | +/-S9 | - | |
| TA100, 1535 (base pair) | 0-3276.8 µg/plate | o-CNB | - | - | Shimizu et al., 1983 |
| | | p-CNB | - | + | |
| | | m-CNB | +/-S9 | - | |
| TA98, 100, 1537, 1538 | up to 5 mg/ plate | m-CNB | +/-S9 | - | Simmon et al., 1977 |
| TA98 | 100 µg/plate | o-CNB | +/-S9 | - | Suzuki et al., 1983 |
| | | p-CNB | +/-S9 | - | |
| | | m-CNB | +/-S9 | - | |
| | | o-CNB | +/S9 and 200 mg norharmon | + | |
| | | p-CNB | | + | |
| TA100 | 100 µg/plate | o-CNB | - | - | Suzuki et al., 1983 |
| | | p-CNB | - | - | |
| | | m-CNB | - | - | |

NR = Not reported

## 5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of o-, m- or p-CNB were not located in the available literature as cited in Appendix A.

## 5.5. CHRONIC TOXICITY

Valisenko and Yumash (1969) examined hematological variables in 135 workers exposed to aniline and CNB. These individuals had reduced prothrombin activity, and decreased levels of fibrinogen and Factor VII. No other details were given in this abstract.

There were no compound-related effects on conditioned reflexes, blood, or liver and kidney function in rats receiving (route not specified) CNB (0.25, 0.005 or 0.0025 mg/kg of o-, m- or p-, respectively) for 7 months. No other details were given in the abstract, which was translated from a Russian study (Davydova, 1967).

In another Russian study, Andreeshcheva (1970) exposed unspecified organisms to m-CNB by inhalation for 98 days. The daily duration of exposure was not specified. The threshold for "nervous system effects" was 0.008 mg/m$^3$.

Nogawa (1961) observed that a single s.c. injection of p-CNB (0.5 g/kg) caused methemoglobinemia and the formation of Heinz bodies in the blood of rabbits. Injection of 0.1 g p-CNB/kg/every 4 days caused similar effects but the animals developed a "resistance" after 3-6 months of treatment.

## 5.6. OTHER RELEVANT INFORMATION

Acute toxicity data for the CNBs are summarized in Table 5-5.

Single or repeated s.c. injection of p-CNB (50-500 mg/kg) has been observed to cause methemoglobinemia, Heinz body formation in the blood, and anemia in rats and rabbits (Zvezdai, 1972; Vasilenko and Zvezdai, 1972;

TABLE 5-5

Acute Toxicity of CNB Isomers

| Compound | Route | Species | $LD_{50}$ (mg/kg) | Reference |
|---|---|---|---|---|
| o-CNB | oral | rat | 288 | RTECS, 1984 |
| o-CNB | oral | rat (M) | 270 | Vernot et al., 1977 |
| o-CNB | oral | mouse | 135 | RTECS, 1984 |
| p-CNB | oral | mouse | 650 | RTECS, 1984 |
| p-CNB | oral | rat (M) | 810 | Vernot et al., 1977 |
| p-CNB | oral | rat | 420 | RTECS, 1984 |
| p-CNB | i.p. | rat | 420 | RTECS, 1984 |
| p-CNB | s.c. | rat | 16,000 | RTECS, 1984 |
| m-CNB | oral | rat | 470 | RTECS, 1984 |
| m-CNB | oral | mouse | 380 | RTECS, 1984 |

M = male

Nishida et al., 1982; Hasegawa and Sato, 1963; Nogawa, 1961). In a study that employed germ-free and conventional rats, Carr et al. (1979) demonstrated that p-CNB (26-28 g/kg, i.p.) produced methemoglobinemia only in the presence of intestinal flora. In a Russian abstract, Alishev and Osipov (1966) reported that m-CNB is absorbed through the skin, and also causes methemoglobin formation. No other details were given. Information regarding the hematological effects, if any, of o-CNB were not located in the available literature.

In an abstract of a Russian study, Labunskii (1972) reported that exposure to p-CNB caused general cardiovascular effects. Rabbits given a single i.p. injection (0.5 g/kg) had reduced blood pressure and levels of myocardial glycogen. Subacute oral doses (unspecified) caused an "increased weight coefficient of the heart and decreased the rhythm of cardiac contractions in rats."

p-CNB has also been shown to inhibit cellular respiration in cultured Ehrlich Ascites cells and V79 lung cells in the presence of glucose (Biagalow et al., 1978). Furthermore, p-CNB was shown to inhibit directly the reduction of ferricytochrome ($C + C_1$), presumably by acting as an electron acceptor.

Kimes and Carr (1982) reported that p-CNB inhibited monoamine oxidase in rabbit liver in vitro. As in the case of ferricylochrome, inhibition of monoamine oxidase is thought to be due to the ability of p-CNB to function as an electron acceptor.

Shimizu (1957) reported that p-CNB affects phosphoric acid metabolism. $^{32}P$ was used to trace phosphoric acid metabolism in animals (unspecified) injected subcutaneously with a 5% solution of p-CNB. After an interval of

12 hours to 5 days following injection of p-CNB, $^{32}P$ was injected, and the blood, pancreas, and liver were examined subsequently for radioactivity. As a result of pretreatment with p-CNB, phosphate associated with RNA was decreased, while phosphate associated with DNA was increased.

## 6. AQUATIC TOXICOLOGY

### 6.1. ACUTE EFFECTS

The acute 96-hour $LC_{50}$ of m-CNB was reported to be 1.2 ppm in the bluegill sunfish Lepomis macrochirus, and 0.55 ppm in the tidewater silverside, Minidia beryllina, in static exposures (Dawson et al., 1975/77).

### 6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic exposure to CNB were not located in the available literature as cited in Appendix A.

### 6.3. PLANT EFFECTS

Pertinent data regarding the effects on plants of exposure to CNB were not located in the available literature as cited in Appendix A.

### 6.4. RESIDUE

Residues of CNB have been found in the edible tissues of fish taken from the Mississippi River downstream from a manufacturing site (Yurawecz and Puma, 1983). Mean levels of o-CNB and p-CNB from four catfish collected near the probable source of discharge were 0.048 ppm and 0.122 ppm, respectively. A composite sample from a carp and sucker contained 0.12 ppm, 0.057 ppm and 0.63 ppm of the o-, m- and p- isomers, respectively. A buffalofish 60 miles downstream contained 0.12 and 0.20 ppm of the o- and p- isomers. At 150 miles downstream, two catfish contained an average of 0.016 ppm o-CNB and 0.022 ppm of p-CNB.

## 7. EXISTING GUIDELINES AND STANDARDS

The Occupational Safety and Health Administration has adopted a TWA of 1 mg/m³ as the standard for occupational exposure to p-CNB (Code of Federal Regulations, 1981).

The ACGIH (1983) also recommends tentatively (pending new studies) a TWA of 1 mg/m³ for occupational exposure to p-CNB.

Davydova (1967) reported an organoleptic threshold of 0.02 mg/ℓ for the various isomers of CNB in drinking water.

## 8. RISK ASSESSMENT

Limited information regarding the chronic toxicity of m-CNB was located in the available literature. There is, however, a body of evidence from the foreign literature that demonstrates that subcutaneously injected p-CNB causes methemoglobinemia and anemia in rats and rabbits (Nogawa, 1961, Zvezdai, 1972; Vasilenko and Zvezdai, 1972; Nishida et al., 1982; Hasegawa and Sato, 1963; Carr et al., 1979). The hematological effects of ingested or inhaled m-CNB have not been investigated satisfactorly.

Weisburger et al. (1978) reported that dietary exposure to o-CNB caused a significant increase ($p \leq 0.025$, Fisher's Exact Test, for both pooled and matched controls) in the incidence of hepatocellular carcinoma in female mice, but not in male mice or male rats. These investigators also reported that dietary exposure to p-CNB caused a significant increase ($p \leq 0.025$, Fisher's Exact Test, for both pooled and matched controls) in the incidence of vascular tumors (unspecified) in both male and female mice at the highest dose tested (TWA = 669 mg/kg/day). p-CNB had no compound-related carcinogenic effects in male rats. According to proposed EPA (1984) quidelines these iosmers can be classified as 132 compounds. Based on these data, it is appropriate to derive $q_1^*$ values for both p- and o-CNB based on these studies. The data from which the $q_1^*$ values were derived are presented in Appendix B. Values of $q_1^*$ derived from the linearized multistage model adopted by the U.S. EPA (Federal Register, 1980) are summarized in Table 8-1. The conversion factor used in the calculation of the human $q_1^*$s from the animal data was the cube root of the body weight ratio, which has been demonstrated empirically to adjust for species-to-species extrapolation (Federal Register, 1980). The highest human $q_1^*$ value for o-CNB is $2.54 \times 10^{-2}$ mg/kg/day, estimated from the incidences of hepatocellular

TABLE B-1

$q_1^*$ Values for Monochlorobenzenes
Producing Tumors in CD-1 Mice[a]

o-CNB: hepatocellular carcinoma

| Species | Sex | $q_1^*_H$ |
|---|---|---|
| Mouse | F | $2.5407 \times 10^{-2}$ mg/kg/day (matched controls) |
| Mouse | F | $2.4826 \times 10^{-2}$ mg/kg/day (pooled controls) |

p-CNB: vascular tumors

| Species | Sex | $q_1^*_H$[b] |
|---|---|---|
| Mouse | F | $1.6394 \times 10^{-2}$ mg/kg/day (matched controls) |
| Mouse | F | $1.3109 \times 10^{-2}$ mg/kg/day (pooled controls) |
| Mouse | M | $1.7697 \times 10^{-2}$ mg/kg/day (matched controls) |
| Mouse | M | $1.5683 \times 10^{-2}$ mg/kg/day (pooled controls) |

[a]Source: Federal Register, 1980

[b]human $q_1^*$ value derived from $q_1^*_A$ (see Appendix B)

carcinoma in treated female mice using matched controls, and for p-CNB is $1.77 \times 10^{-2}$ mg/kg/day, estimated from the incidences of vascular tumors in treated male mice using matched controls.

The lack of information regarding the chronic toxicity or carcinogenicity of m-CNB precludes derivation of an ADI or a $q_1^*$ for this isomer.

## 9. REPORTABLE QUANTITY RANKING BASED ON CHRONIC TOXICITY

The lack of adequate chronic toxicity studies for the m-CNB precludes derivation of reportable quantities for this isomer (Table 9-1). The available studies (see Section 5.5.) either were designed primarily to investigate the hemolytic effects of repeated subcutaneous exposure (Nogawa, 1961) or were abstracted from the Russian literature and were insufficiently detailed to draw any reliable conclusions (Vasilenko and Yunash, 1969; Davydova, 1967; Andreescheva, 1970).

Weisburger et al. (1978) tested the carcinogenicity of the o- and p- isomers of CNB in rats and mice. Although data regarding carcinogenicity were adequately detailed, parameters of toxicity were not reported; hence CSs cannot be calculated from these studies.

TABLE 9-1

Chloronitrobenzene (o-, m- or p-)

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:

Dose

Effect:

Reference:

$RV_d$

$RV_e$:

Composite Score:

RQ: Data are insufficient to derive RQs for any of the CNB isomers.

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## APPENDIX A

## LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:


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APPENDIX B[a]

| Sex | Compound/Tumor | Experimental Doses (ppm)[b] | Transformed Doses (mg/kg/day)[b] | Tumor Incidence | $q_1^*_A$ (mg/kg/day)$^{-1}$ | $q_1^*_H$[c] (mg/kg/day)$^{-1}$ |
|---|---|---|---|---|---|---|
| F | o-CNB/ hepatocellular carcinoma | 0 | 0 | 0/20 (matched controls) | 1.2848 $(10)^{-3}$ (matched) | 2.5407 $(10)^{-3}$ (matched) |
| | | 0 | 0 | 1/102 (pooled controls) | 1.2554 $(10)^{-3}$ (pooled) | 2.4826 $(10)^{-3}$ (pooled) |
| | | 2167 | 242 | 5/22 | | |
| | | 4333 | 483 | 5/19 | | |
| F | p-CNB/ vascular tumors | 0 | 0 | 0/15 (matched controls) | 8.2899 $(10)^{-4}$ (matched) | 1.6394 $(10)^{-3}$ (matched) |
| | | 0 | 0 | 9/102 (pooled controls) | 6.6291 $(10)^{-4}$ (pooled) | 1.3109 $(10)^{-3}$ (pooled) |
| | | 3000 | 334 | 2/20 | | |
| | | 6000 | 669 | 7/18 | | |
| M | p-CNB/ vascular tumors | 0 | 0 | 0/14 (matched) | 8.9488 $(10)^{-4}$ (matched) | 1.7697 $(10)^{-3}$ (matched) |
| | | 0 | 0 | 5/99 (pooled) | 7.9304 $(10)^{-4}$ (pooled) | 1.5683$(10)^{-3}$ (pooled) |
| | | 3000 | 334 | 2/14 | | |
| | | 6000 | 669 | 4/14 | | |

[a]Data from mice (Weisburger et al., 1978) were used in the generation of $q_1^*$ values.

[b]Doses were transformed from ppm to mg/kg/day by multiplying ppm x 0.13 (equivalent fraction of body weight consumed in food/day), then multiplied by (te/Le).

[c]$q_1^*_H = q_1^*_A\ (L/Le)^3\ (70/W_A)^{1/3}$, where 70 kg = weight of the standard man.

For all experiments

Duration of exposure (te): 548 days

Length of experiment (Le): 639 days

Lifespan of animal (L): 730 days

Weight of animal ($W_A$): 0.03 kg